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REVIEW

ANIMAL MODELS OF EATING DISORDERS

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Abstract—Feeding is a fundamental process for basic survival and is influenced by genetics and environmental stressors. Recent advances in our understanding of behavioral genetics have provided a profound insight on several components regulating eating patterns. However, our understanding of eating disorders, such as anorexia nervosa, bulimia nervosa, and binge eating, is still poor. The animal model is an essential tool in the investigation of eating behaviors and their pathological forms, yet development of an appropriate animal model for eating disorders still remains challenging due to our limited knowledge and some of the more ambiguous clinical diagnostic measures. Therefore, this review will serve to focus on the basic clinical features of eating disorders and the current advances in animal models of eating disorders.

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Key words: animal models, eating disorders, anorexia, bulimia, binge eating, obesity.

Contents

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Abbreviations: AAPD, atypical antipsychotic drug; ABA, activity-based anorexia; AgRP, agouti-related hormone; AN, anorexia nervosa; ARC, arcuate nucleus; BDNF, brain-derived neurotropic factor; BED, binge eating disorder; BN, bulimia nervosa; CART, cocaine-amphetamine-regulated transcript; CSF, cerebrospinal fluid; DA, dopamine; HFD, high-fat diet; LH, lateral hypothalamus; MCH, melanin-concentrating hormone; MSH, melanocyte-stimulating hormone; NPY, neuropeptide Y; POMC, proopiomelanocortin; PVN, paraventricular; SNP, single nucleotide polymorphism.

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Energy homeostasis is essentially a balancing act between food intake and energy expenditure via basic metabolism or physical activities (Feige and Auwerx, 2007; Gao and Horvath, 2007). Eating disorders, such as anorexia nervosa, bulimia nervosa, and binge eating, are described as disturbances in eating habits usually involving insufficient or excessive food intake. These abnormal eating patterns cause energy imbalance, resulting in the detriments to the individual's well-being (Sodersten et al., 2006; Thornton et al., 2011; Weiselberg et al., 2011). These disturbances are not limited to alteration of diet choices but also include abnormal psychological perceptions towards food, eating, body weight, and self-image. The etiology of eating disorders has yet to be characterized, but it is evident that the cause is multifactorial. The current identified causes of eating disorders are cultural pressures, biology, environment, and genetic predisposition (Sodersten et al., 2006; Weiselberg et al., 2011).

Animal models have been a powerful tool in researching neuropsychiatric conditions (Fernando and Robbins, 2011; Sarnyai et al., 2011). A well-characterized etiology is always a good basis for developing appropriate animal models for any disease state. For example, if genome-wide association studies have provided a potential risk gene for a disease in humans, the homologous genes can usually be easily mutated or deleted in animal models (Fernando and Robbins, 2011). While the causes of some diseases may not always be characterized, the understanding of disease progression and treatment may be useful in developing an effective animal model. Unfortunately, the lack of such information has hampered the efficient utilization of animal models to investigate eating disorders (Casper et al., 2008; Smith, 1989). Moreover, due to the complex nature of eating disorders, current animal models can only provide a few characteristic traits of the human psychiatric disease. Despite this setback, many scientists in the field are able to develop powerful paradigms to study specific aspects of eating disorders.

In this review, the clinical, behavioral, and physiological features of anorexia nervosa, bulimia nervosa, binge eating disorder, as well as obesity, although not specifically characterized as an eating disorder, will be discussed, followed by the understanding of how scientists can recapitulate these conditions in animal models. This will be followed by an overview of utility and limitations of the different available animal models for eating disorders and obesity relevant to the human condition.

One of the major hurdles animal models face is that they cannot show multiple traits of human psychiatric diseases. As

an alternative approach, nonhuman primate models have been utilized to investigate the complex behavioral, social, and genetic interactions (Nelson and Winslow, 2009). However, these nonhuman primate models have their own disadvantages; (1) nonhuman primates are much more expensive to maintain than nonprimates, (2) it is extremely time consuming to develop their model systems, and (3) behavior testing in primates is not standardized. Even with these limitations, nonhuman primate models have contributed greatly to certain experimental questions addressing social and complex cognitive interactions. Because of these drawbacks to the usage of nonhuman primates as models of eating disorders, it is necessary to develop other, more practical, vertebrate animal models.

ANOREXIA NERVOSA

Anorexia nervosa (AN) is the most common eating disorder that primarily affects teenage girls at puberty. It is characterized by chronic food refusal, excessive weight loss, an intense fear of weight gain and a distorted self-image including body shape and weight (American Psychiatric Association, 2000; Attia, 2010; Weiselberg et al., 2011). It usually manifests with an innocent effort to reduce caloric intake, which gets out of control. Individuals with AN continue to feel hunger, yet deny themselves by restricting food intake (Attia, 2010; Garfinkel, 1974). The first major clinical symptoms are derived from psychological changes, which can be characterized as motivated refusal to eat and maintain a body weight above 85% of the standards, intense fear to gain weight. These symptoms can be exacerbated by physiological and endocrine changes caused by the shortage of food or energy intake. A significant weight loss below 85% of normal weight for age and height or a body mass index below 18 is generally the first noticeable signs of AN (American Psychiatric Association, 2000; Hebebrand et al., 2004). Obviously, the extreme weight loss associated with AN can lead to endocrine disturbances such as amenorrhea, the absence of menstrual periods for postpubertal females. Also, plasma leptin level, which normally is secreted from adipose tissue after feeding, is reduced in AN patients (Hebebrand et al., 2003; van Elburg et al., 2007). Most of the endocrine changes that influence the regulatory system in AN are a reflection of the body's adaptation to an extended exposure to malnutrition (Casper and Davis, 1977). Many people going through prolonged starvation due to either religious or clinical reasons experience fatigue and slowed activity levels (Casper, 1998). However, individuals with AN tend to exhibit high activity levels, as well as mental alertness, during their weight loss from food restriction. This in turn drives them to engage in excessive exercise, creating a detrimental positive feedback/reward cycle (Casper, 1998; Casper et al., 1991; Klein et al., 2007; Pirke et al., 1991).

AN patients commonly display comorbid psychiatric symptoms such as anxiety, obsessive-compulsive disorders, and depressive disorders (Attia, 2010; Casper and Davis, 1977; Casper et al., 1979; Mattar et al., 2011; Ploog and Pirke, 1987). Malnutrition is thought to augment these symptoms because the disturbance of neurotransmitter levels is restored after nutritional restoration. One of the classical studies by Keys et al. also showed that these psychiatric symptoms can be derived from malnutrition (Keys et al., 1950). In this study, healthy male volunteers were subjected to a semistarvation condition for 3 months. The group showed not only the typical physiological changes due to malnutrition but also psychiatric symptoms such as depression, obsessive-compulsive like, and psychosis-like behaviors, which are very common among patients with eating disorders (Keys et al., 1950). Since the publication of this study, it has been debated whether psychiatric symptoms observed in patients with AN, or any eating disorder, are the cause or consequence of malnutrition.

Recent studies have illustrated that most people with AN (or other eating disorders) show childhood anxiety and perfectionism or obsessive-compulsive, personality patterns prior to the onset of an eating disorder (Lilenfeld et al., 2006). These studies suggest that patients displaying these symptoms may be susceptible to developing eating disorders later in life. Malnutrition appears to enhance these premorbid behavioral traits rather than causing them. Moreover, studies have also shown that some traits such as perfectionism, negative emotionality, and harm avoidance (a multifaceted temperament trait that contains elements of anxiety, inhibition, and inflexibility) still persist long after a recovery from AN (Deep et al., 1995).

Patients with AN have significantly reduced cerebrospinal fluid (CSF) serotonin (5-HT) metabolites compared with control subjects (Kaye et al., 2005; Stanley et al., 1985). More recent imaging studies showed that 5-HT_{1A} receptor expression is increased, while 5-HT_{2A} receptor expression is unchanged in both ill and recovered AN patients' brains (Audenaert et al., 2003; Bailer et al., 2007; Galusca et al., 2008). These changes in receptor expression may be a compensatory mechanism to respond to a decrease in 5-HT levels. An increase in food intake, in particular carbohydrate intake, enhances extracellular 5-HT levels. This change may potentiate the effect of 5-HT_{1A}, which is positively associated with harm avoidance in patients suffering from AN. Therefore, it is possible to speculate that malnutrition in AN patients has reduced 5-HT levels and consequently decreased dysphoric mood. Despite numerous studies supporting the involvement of 5-HT in AN, serotonin reuptake inhibitors (SSRIs) showed very limited success in reducing moods or other core psychiatric symptoms in AN patients (Attia and Schroeder, 2005). Nevertheless, it is tempting to speculate that imbalances between 5-HT_{1A} and 5-HT_{2A} contributes at least in part to such traits of AN, but further studies are needed to make this conclusion.

People with AN engage in exercise compulsively, and this trait also tends to remain after recovery (Klump et al., 2004; Shroff et al., 2006). The dopamine (DA) pathway plays a critical role in compulsive and addictive behavior. Recently, it has been shown that DA metabolites in ill and recovered AN individuals are reduced in CSF (Kaye et al., 1999). Also, positron emission tomography (PET) studies show that those who recovered from AN had increased

D2/D3 receptor expression in ventral striatum, an area that responds to reward stimuli (Frank et al., 2005). In particular, DA in ventral striatum plays a role in motivational aspects to stimuli (Montague et al., 2004; Schultz, 2004). Alternation of DA system in this area may explain the difficulty of motivating AN patients for treatment. While typical and atypical antipsychotic drugs target the DA system, previous studies examining the effect of typical antipsychotic drugs whose target is limited to DA system did not show any significant changes in food intake (Lambert and Porter, 1992). However, atypical antipsychotic drugs, (AAPDs) would be exciting drugs to examine for this disorder and deserve further studies. AAPDs interact not only with DA but also with 5-HT (Miyamoto et al., 2005). One of the side effects of AAPDs is weight gain (Ananth et al., 2004; Newcomer, 2005; Teff and Kim, 2011), which would be a welcomed effect for patients with AN. Current studies show that olanzapine treatment induces a decrease in anxiety and depression in AN patients (Bissada et al., 2008), but a larger scale study is required to determine whether this type of AAPD has any effect on improving food consumption in AN patients.

Animal models

Self-starvation/activity-based anorexia (ABA). Self-motivated caloric restriction is characteristic of eating disorders, especially in AN. Many animal models fail in this aspect because food intake is controlled by experimenters. However, in a self-starvation model, an environment is created such that animals must "choose" between food intake or another rewarding condition such as brain stimulation or exercise.

Activity-based anorexia (ABA) is an animal model that recapitulates a subset of key characteristics of AN, especially hyperactivity and reduced food intake. Considering main physiologic characteristics, reduced body weight in AN, it is not surprising to see a significant reduction in leptin levels, as leptin is an adipose-derived hormone (Leibowitz and Wortley, 2004; Wynne et al., 2005). AN patients also exhibit reduced leptin levels in plasma and CSF (Exner et al., 2000; Holtkamp et al., 2006). Upon leptin administration to ABA rodents or AN patients, hyperactivity was suppressed (Hillebrand et al., 2005). The mechanism underlying hyperactivity in AN despite a negative energy balance is still unclear. ABA is also known as semistarvation-induced hyperactivity or activity anorexia. Activity-induced hypophagia was initially introduced in 1967 using running wheels (Routtenberg and Kuznesof, 1967). This model reproduces the following main hyperactivity behaviors characteristic of AN: reduced food intake in the presence of hunger, weight loss, desire for activity along with physiological responses of malnutrition. Under a restricted food schedule, such as 60 min of feeding per day, ABA rodents still maintain normal body weight (Avraham et al., 2001a; Routtenberg and Kuznesof, 1967). However, once a running wheel is introduced at all times except for the time when they eat, their food intake gradually starts to decrease. Eventually, energy expenditure by wheel running exceeds caloric intake, and they starve themselves to death. In contrast to ABA rodents, control *ad libitum* fed rats with continuous access to running wheels show stable levels of running wheel activity, as well as an increase in food intake, to compensate for increased energy expenditure (Kas et al., 2003). Moreover, control rats on a restricted feeding schedule without running wheels exhibit an increased food consumption and marginal body weight loss compared with ABA rats (Kas et al., 2003). ABA rats are a very relevant model mimicking AN, as these animals can overcome the basic homeostatic mechanism for survival under this model.

Furthermore, female ABA rodents exercised more than male rats during the starvation–exercise model (Pirke et al., 1993). Under this activity model, decreased food intake is associated with the increased 5-HT levels in hypothalamus similar to stress models (Avraham et al., 2001a). This gender difference is also an area requiring further investigation, as it correlates with human distribution of AN among genders. Routtenberg et al. showed that when ABA rats were given a choice between eating food and pressing a lever for positively reinforcing electrical stimulus in posterior hypothalamus, rats chose stimulation reward (Routtenberg and Kuznesof, 1967). This experiment strongly implicates that patients with AN may have imbalances in the reward system influenced by distorted self-image or societal pressures and gain more pleasure from weight loss than maintaining a healthy life style (Casper et al., 1979; Eckert et al., 1979; Ploog and Pirke, 1987).

Stress models. Stress-mediated changes in hypothalamus–pituitary–adrenal axis (HPA) can affect food intake (Jahng, 2011; Lo et al., 2008). Indeed, it has been reported that hormonal imbalances in the HPA via a life stressor are frequently involved with some forms of eating disorders. The stress-mediated eating behavior is one of the most widely used models because it does not require the manipulation of food availability. There are many stress models, such as cold swimming, tail pinching, and direct brain stimulation, that can induce weight loss in animals (Shimizu et al., 1989; Wilson and Cantor, 1986). It is well known that stress can lead to weight loss and contribute to a loss of appetite but caution must be taken into consideration when utilizing such models to study AN, as excessive manipulation such as electrical stimulation of the brain can physically harm the animals. In recent years, severe and mild forms of stressors have been introduced to induce weight loss in animal models. One example is the novelty environment, wherein mice are introduced to surroundings to which they have not been previously exposed. Utilizing this model, Asaka's group showed that corticotropin-releasing factor is activated, and subsequently, peripheral levels of ghrelin, orexigenic peptides are reduced (Saegusa et al., 2011).

Physical isolation can induce a depression-like condition with reduced food intake and cognitive function. Mice are housed in a cage with individual partitioning so that they can see and smell each other without physical contact except at feeding time. This model overcomes some shortcomings of other stress models to induce weight loss, as it

does not involve any physical harm to animals. Previous studies show that separation-mediated stress decreases DA and norepinephrine levels in the hippocampus. It appears that this stress-mediated loss of appetite is induced by increased 5-HT levels in the hypothalamus, as administration of 5-HT receptor antagonist prevents weight loss under these conditions. However, it is important to point out that it is unlikely that stress-mediated imbalance of 5-HT itself is a direct cause of AN even though it can trigger weight loss. In particular, individuals with AN appear to have reduced 5-HT levels.

Diet restriction. It has been shown that caloric restriction extends life span in various laboratory animal species, with improvement of many pathological genetic changes during aging (Spindler, 2010). However, excessive food restriction of less than half of daily *ad libitum* intake can be used as an AN model. A significant drawback to this model is that, unlike individuals with AN, food restriction is not voluntary. Nevertheless, many of changes in the neuro/endocrine systems observed in AN can be mimicked by diet restriction alone in mice. Under the chronic food restriction model, rats exhibited reduced cognitive function (Campbell and Bedi, 1989; Idrobo et al., 1987; Yokogoshi and Nomura, 1991). Tyrosine supplementation in this model improved cognitive function without changing body weight (Avraham et al., 2001b). This may have important implications in treating patients with AN, as many patients frequently do not respond well to psychological treatments during nutritional rehabilitation, which is typically accompanied by weight gain (Attia, 2010; Avraham et al., 2001b; Casper, 1998).

Genetic model. A remarkable flurry of genetic research pertaining to eating behaviors in the past decade has identified a large number of novel genes whose products are important players in regulating food intake and energy balance. Many animal models mutating these targets genes produce an obesity phenotype, which will be briefly discussed later in this review although it is not considered an eating disorder. The obesity gene functions are well characterized in animal models, yet very few anorexia or hypophagia genetic models are available. Moreover, there is no direct evidence to correlate genetic alternation to human AN. Nevertheless, this has clear advantages. In a genetic model, specific genes that may lay on the potential pathways contributing to etiology of AN can be directly examined. Moreover, genetic modifications generate more stable and reproducible phenotypes.

The most commonly studied genetic model of AN is anx/anx mice. The autosomal recessive anx mutation in rodents is reported to have decreased food intake behaviors, so extreme it causes death within 20–30 days after birth (Johansen et al., 2003). Moreover, the mice are characterized by reduced body weight, body tremors, head weaving, hyperactivity, and uncoordinated gait. These mice have reduced serum leptin levels and show abnormalities in the orexigenic (neuropeptide Y [NPY] and agouti-related hormone [AgRP]) and anorexigenic (proopiomelanocortin [POMC] and cocaine-amphetamine-regulated transcript [CART]) pathways (Broberger et al., 1998, 1999; Johansen et al., 2000). In particular, immunohistochemical analysis revealed that NPY and AgRP neuropeptides are accumulated in cell bodies rather than dendrites of affected animals. Considering that leptin, which is produced in adipose tissue and modulates these neuropeptides, is lacking in anx/anx rodents, it is not too surprising to observe deregulation of these neuropeptides (Zarate et al., 2004). A recent study revealed that anx/anx mice displayed hypothalamic degeneration accompanied by inflammatory responses (Nilsson et al., 2011; Saegusa et al., 2011), and they fail to regulate food intake. This raises a slight concern about this model for AN, as individuals with AN typically feel hunger and yet refuse to consume food unlike the anx/anx mouse model.

Brain-derived neurotropic factor (BDNF) plays various key roles helping to support the survival of existing neurons and promote the growth and differentiation of new neurons and synapses (Nagahara and Tuszynski, 2011). Ribases et al. explored the possibility of BDNF as a potential gene associated with AN after observing that BDNF knockout leads to an increased food intake, while intraventricular administration of BDNF results in reduced food intake and weight loss in rats (Ribases et al., 2003). They also reported a strong correlation between weight loss induced by restricting AN and a point mutation in BDNF (Val66Met). However, recent studies failed to demonstrate the preferential transmission of the 66Met allele of BDNF in AN (Brandys et al., in press; Dardennes et al., 2007).

Several neurotransmitters have been proposed to be perturbed in eating disorders, but monoamine systems, in particular DA and 5-HT pathways, have been researched most extensively. Recent imaging studies with PET showed altered serotonergic and dopaminergic neuronal pathway activities (Frank et al., 2005; Kaye et al., 1999). Dopamine deficient (DD) mice lacking the DA-synthesizing enzyme, tyrosine hydroxylase, in dopaminergic neurons become hypophagic and hypoactive and die of starvation at 34 days (Szczypka et al., 2001). Their phenotypes can be reversed by daily administration of L-DOPA or by viral gene delivery of tyrosine hydroxylase (Hnasko et al., 2006).

It is established that disturbances in opioid receptors are associated with feeding. Because of this association, it is likely to play a role in AN. Moreover, a recent genome-wide association study further confirmed that delta opioid receptor (OPRD1) is a risk gene (Brown et al., 2007). Studies have shown that disturbances in OPRD1 receptors can lead to an auto-addiction to fasting and exercise. Mouse models with OPRD1 receptor genes knocked out can be a useful tool in analyzing this aspect of eating disorders (Rask-Andersen et al., 2010). When the ligand for OPRD1, orphanin FQ, is injected to rats, it induces hyperalgesia and induces feeding in satiated animals. When an antagonist is introduced to this system, feeding is inhibited and returned back to normal (Pomonis et al., 1996).

Feeding behavior and satiation is also affected by seretonergic neurotransmission. 5-HT stimulation, via agonist

in mice, inhibits food intake, suggesting that 5-HT is associated with satiety (Mancilla-Diaz et al., 2005). In both animal models and humans, agonist stimulation decreases the rate and meal size. 5-HT_{1B} seems to be responsible for the amount of food intake, while 5-HT_{2C} controls rate of eating. However, drugs that induce 5-HT_{1A} increase food intake (Simansky, 1996). Because of this multifactorial response, animals with genetic deletion of different 5-HT receptors act as a good genetic model to study AN and binge eating disorder (BED).

Mice deficient of the M3 muscarinic receptor (M3R−/−) show a decrease in food intake and subsequent reduced body weight, low levels of serum leptin and insulin, and a significant elevation in basal and total energy expenditure (Qu et al., 1996; Shimada et al., 1998). In these mice, AgRP levels are elevated, while POMC is decreased. This appears to be a reflection of the negative energy balance. Interestingly, hypothalamic melanin-concentrating hormone (MCH), which promotes feeding, is significantly reduced in these mice. The combination of the reduced expression of MCH, as well as a lack of AgRP activity, plays major role on the hypophagic phenotype in these mice. Mice that lack MCH have a hypophagic phenotypes and an increased metabolic rate. These mice have normal levels of orexigenic peptides such as AgRP and NPY, but POMC is reduced even though leptin levels are decreased. M3R−/− mice are more susceptible to weight loss after food deprivation compared with wild-type mice, and majority of MCH deleted mice die after 48 h of starvation (Shimada et al., 1998).

Despite limited proof of a specific genetic component, evidence supports a strong genetic correlation in susceptibility to AN. A recent study by Wang et al. identified common single nucleotide polymorphisms (SNPs) within the *OPRD1* gene (rs533123) that confer risk for AN and obtained suggestive evidence that common SNPs near the *HTR1D* gene (rs7532266) impart risk for restricting-type AN. This evidence suggests that both common SNPs and rare CNVs may pose a genetic risk for AN (Wang et al., 2011). Compared with other psychiatric disorders, AN is more likely to be associated with sociocultural differences, which complicates traditional genetic studies, but identification of these susceptibility gene(s) by genome-wide association study will help researchers design appropriate animal models.

BULIMIA NERVOSA/BINGE EATING

Bulimia nervosa (BN) is described as recurrent episodes of binge eating at least twice weekly for 3 months, with a sense of inability to control overeating also associated with repeated compensatory behaviors such as vomiting and excessive exercise (American Psychiatric Association, 2000; Mathes et al., 2009). Unlike AN, which has a long-documented history, BN is a relatively new syndrome, first described in 1979 (Russell, 1979). In Diagnostics and Statistical Manuals for Mental disorders-V (DSM-V), the binge-eating phase of BN is characterized by both of the following: first, an affected person will binge eat in a defined period of time, an amount of food that is much larger than what most people would eat during a similar period of time and under similar circumstances. Second, the affected individual has one of five traits; (1) a lack of control over eating during the binge episode, (2) recurrent inappropriate compensatory behavior, such as self-induced vomiting, fasting, and excessive exercise, in order to prevent weight gain or a misuse of laxatives or other medications, (3) the binge eating and inappropriate compensatory behaviors both occur, on average, at least once a week for 3 months, (4) self-evaluation is primarily influenced by body shape and weight, and (5) the binge disturbance does not occur during episodes of AN (http://www.dsm5.org/). BN exhibits a high comorbidity with affective disorders (Brewerton et al., 1995); substance abuse is frequently associated with BN (Strober et al., 1999). Furthermore, it appears that patients with a BN history are more sensitive to stress than those with AN, suggesting that a stressful environment can easily trigger binge eating.

A similar eating disorder to BN is BED, which has similar diagnostic criteria as BN, a large amount of consumption, or a loss of self-control. In addition, a definition of "binge" in either BED or BN also includes temporal dimension such as within the 2-h period for food consumption (Cooper and Fairburn, 2003; Latner and Clyne, 2008; Wolfe et al., 2009) once a week for 3 months. However, diagnosis of BED has to be associated with at least three characteristics; (1) eating much more rapidly than normal, (2) eating until feeling uncomfortably full, (3) eating large amounts of food when not feeling physically hungry, (4) eating alone because being embarrassed of how much one is eating, and (5) feeling disgusted with oneself and depressed or very guilty after overeating (American Psychiatric Association, 2000). Moreover, binge eating in BED is not associated with the regular use of inappropriate compensatory behaviors (Cooper and Fairburn, 2003). Although BN and BED share many clinical symptoms, they have distinct diagnostic criteria that are the primary basis to develop separate animal models. Notably, traits, such as binge eating for 6 vs. 3 months or a lack of compensatory behavior in BED, that differentiate the two disorders are impossible to recapitulate in animal models; therefore, BED and BN appear to share the same animal models until other characteristics, which can be manipulated in a laboratory setting, such as different susceptible genes can be explored.

Food restriction

Food restriction or deprivation can induce increased food intake in animals. It has been shown that as little as 2 h of food restriction can trigger an increase in subsequent food consumption in rats. (Cottone et al., 2008; Hagan et al., 2003). Increased food consumption is apparent within 2 h of food restriction; after reintroducing food, a "binge-like" food intake persists for at least 4 h. Other studies have explored food restriction and refeeding paradigms by exposing animals to repeated fasting episodes to induce moderate weight loss, subsequently followed by periods of refeeding for animals to regain their normal weight levels

(Hagan and Moss, 1991; Specker et al., 1994). When animals lost 20–35% of their normal weight, the animals showed significant binge-like eating, even in sated state. This behavior can be induced in the absence of any additional factors such as palatable food or an environmental stressor. However, there are a few points we must first consider; a simple increase in food consumption is different from "binge" eating. Second, binge eating is not usually driven by physical hunger (American Psychiatric Association, 2000; Waters et al., 2001). Even with the drawbacks on food restriction model, it still provides interesting aspects of eating disorders. The increase in food intake observed after fasting persists even after meeting basic metabolic needs, which reflects one characteristic of binge eating in humans (Hagan et al., 2003). Nevertheless, it is important to point out that dieting and food restriction have been shown to increase the risk of binge eating in individuals either with or without history of BN or BED (Stice et al., 2001, 2006).

Stress

It is well documented that stress can influence feeding behavior (Jahng, 2011; Lo et al., 2008). Animal models depicting food restriction show increases in food consumption, but the effect was quite moderate. However, when fasting/refeeding paradigm is combined with food shock stress with palatable foods, animals display binge-like increases in caloric intake (Hagan et al., 2002). This binge-like behavior is not expressed if animals are exposed to only fasting/refeeding or food shock (Artiga et al., 2007; Chandler-Laney et al., 2007). In fact, the effect of this combination is quite specific, as animals have to be exposed to at least three cycles of fasting/refeeding cycles before food shock in order to induce binge-like behavior (Artiga et al., 2007). Instead of physical stress such as food shock, environmental factors can be manipulated to introduce stress such as postnatal maternal separation (MS) (Jahng, 2011). Rodents under this stress exhibit depression and anxiety-like behaviors in adulthood, with imbalances in serotonin levels. However, they do not show obvious sign of hyperphagia or weight gain. Once MS is combined with repeated fasting/refeeding cycle during adolescence period, rodents start to display binge-like eating behaviors (Jahng, 2011).

It is interesting to note that stress itself does not always increase food consumption. As a matter of fact, a stress model can also be utilized to study AN as described in this review. At least in human behavior, it appears that the nature of the stressor delineates the outcome of eating behaviors. Physiological stressors such as overloaded work, interpersonal issues, or self-pride have been associated with an increase in food intake or extra snacking between meals (Heatherton and Baumeister, 1991; O'Connor et al., 2008), whereas stressors caused by a threat of physical pain or discomfort displays the opposite behavior (Heatherton et al., 1991).

Therefore, combination of stress and fasting/refeeding paradigm captures some binge eating behaviors, but there are some caveats to it. Binge eating behavior is more severe with palatable food than with normal chow. This leads to speculations that an increase of palatable food consumption under this model serves as an increased motivation for reward after repeated fasting. Finally, none of the models described earlier address one of the core criteria of either BN or BED; the sense of lack of self-control, or the emesis, following the binge-eating of BN.

Sham-feeding

There is no rodent model that reproduces postprandial vomiting. However, the sham-feeding model may provide compelling evidence as a behavior model of binge eating. Sham-feeding can be achieved with a gastric fistula, by which liquid food can be drained from the opening before it enters the intestine (Smith, 1989, 1996). Under these conditions, rats show binge-like behavior consuming a large amount of food compared with the controls with fistula closed. This model mimics purging seen in BN. However, it needs to be pointed out that drainage is by experimental manipulation and not by the animal's own intention. Nevertheless, this model can bypass the negative feedback from the intestinal system and offer insight to the physiology associated with BN.

Obesity

Obesity is an increasingly common condition in the United States and worldwide and associated with hypertension, impaired glucose tolerance or diabetes, and dyslipidemia, which are risk factors for cardiovascular morbidity (Rader, 2007). However, is obesity an eating disorder? Eating disorders are defined as disturbances in eating habits that usually involve insufficient or excessive food intake causing energy imbalance. Hence, by this definition, obesity can be caused by abnormal eating habits but also be a consequence, not a cause, of metabolic imbalance. It is important to note that obesity is not classified as a psychological or psychiatric disorder. It is, however, related to eating disorders, and it can be the consequence of BED, an identified eating disorder. Because of this relation, obesity and its animal models will be briefly described in this review. Since genetic components and the signaling pathways involved in obesity are relatively well understood, understanding this disease state and its animal models may provide additional insight to the investigating eating disorders.

Obesity essentially results from the energy imbalance between calories ingested and total calorie expenditure. Energy balance is orchestrated by both the brain and periphery. One of the key regions of the brain involved in regulating this process is the hypothalamus (Gao and Horvath, 2007; Wynne et al., 2005). A set of systemic lesion experiments in rats identified the specific hypothalamic structures that are directly involved in energy homeostasis such as the hypothalamic ventromedial (VMH), paraventricular (PVN) and dorsalmedial (DMH) nuclei as satiety centers, and the lateral hypothalamus (LH) as the hunger center (Berthoud and Morrison, 2008; Sandoval et al., 2008). More recently, genetic deletion studies have enabled us to identify a large number of peptides and signal-

ing cascades within the hypothalamus responsible for these feeding behaviors. Hence, food intake is now believed to be controlled by a neural circuit with specific peptides such as leptin, α-melanocyte-stimulating hormone (α-MSH), NPY, AgRP, and many other neuropeptides (Leibowitz and Wortley, 2004; Wynne et al., 2005).

The arcuate nucleus (ARC) is of particular importance in integrating signals for regulating appetite, as it is easily accessible to circulating signals for energy balance via underlying median eminence (Broadwell and Brightman, 1976). Two subsets of neurons regulating food intake are found in ARC, with opposing effects. The first set of cells express POMC and CART, exerting anorexigenic effects (Boston et al., 1997; Gao and Horvath, 2007; Kristensen et al., 1998). POMC is cleaved and produces MSH (α-, β-, and γ-MSH). Among these, α- and β-MSH increase energy expenditure and suppresse food intake in animals by binding to melanocortin receptor subtype 3 and 4 (MC3/4R), which are particularly abundant in the ARC, PVN, LH, and DMH (Adan et al., 1994; Leibowitz and Wortley, 2004). The other group of neurons modulates orexigenic effects by NPY and AgRP (Baskin et al., 1999; Ollmann et al., 1997). NPY increases food intake and reduces energy expenditure. It is detected throughout the brain but is highly expressed in the ARC region. AgRP is a natural antagonist for MC3/4R and hence can inhibit the anorectic effects of α-MSH (Ollmann et al., 1997).

ARC has neuronal projection to LH, hypothalamic nucleus comprising two distinct neuronal populations containing neuropeptides, orexin, and MCH (Qu et al., 1996). Starvation increases the expression of MCH and pre-prooorexin, and intracerebroventricular administration of these peptides enhances food intake (Sakurai et al., 1998). From LH, orexin-containing neurons projects to various brain regions modulating feeding (King, 2006; Qu et al., 1996; Sakurai et al., 1998). VMH is another important hypothalamic site containing BDNF and receives connections from NPY/AgRP and POMC/CART neurons (Unger et al., 2007). The hypothalamus is known to be the classical center for feeding control, but recent studies revealed that other areas such as hindbrain or hippocampus area are also involved in eating behavior (Grill, 2006).

Genetic model

In combination with genetic tools, the contribution of animal models in obesity research is undeniable (Speakman et al., 2008). In particular, recent advances in genetic tools such as the Cre/loxP system has allowed us to manipulate gene expression both spatially and temporally and became a powerful means to elucidate pathways that regulate body weight (Kos, 2004). There are numerous animal models that lead to obesity but describing all of them is out of scope for this review (Johnson et al., 1991; Pomp et al., 2008). Therefore, representative examples that affect eating behavior will be briefly described.

The most representative genetic models of obesity mice are ob/ob and db/db mice. The ob/ob mouse is a genetic model of leptin deficiency caused by a spontaneous mutation in the obese (ob) gene, which encodes leptin (Zhang et al., 1994), while db/db mouse has a mutation in the leptin receptor (Chen et al., 1996). These mice have similar phenotypes such as hyperphagia, profound early-onset obesity, hyperglycemia, insulin resistance, and type 2 diabetes.

The central melanocortin system plays an essential role, controlling energy homeostasis as described earlier. Obese agouti mice (Ay/a) bear a spontaneous mutation producing excess agouti protein, which functions as an antagonist of melanocortin receptor (Miltenberger et al., 1997; Salton et al., 2000). The role of this pathway was also demonstrated by generating MC4R knockout mice that exhibit excess weight gain, hyperphagia, hyperinsulinimea, and increased linear growth (Huszar et al., 1997). Importantly, mutations in the gene encoding MC4R are the most common form of human obesity (Farooqi et al., 2003; Vaisse et al., 2000).

The monoamine histamine is an important chemical messenger that regulates a wide variety of physiologic responses in the brain and peripheral organs (Haas et al., 2008). Four metabotropic histamine receptor types (H1R–H4R) have been cloned so far (Martinez-Mir et al., 1990; Nguyen et al., 2001). H1R–H3R are expressed in abundance in the brain, and H4R mainly occurs in peripheral tissues (Haas et al., 2008). Histamine or H1R agonists injected centrally decrease the level of food intake and enhance *c-fos*-like immunoactivity in the PVN in mice, (Lecklin et al., 1998; Masaki et al., 2004; Orthen-Gambill, 1988), while blockade, as well as genetic deletion of H1R, elicits an increased daily food intake (Sakata et al., 1988), indicating the H1R is important for regulation of energy balance. In addition to the effect on food intake, it has been shown that brain histamine might regulate body weight and adiposity by modulating peripheral energy metabolism in rodents (Masaki and Yoshimatsu, 2006).

Some mouse strains are extremely sensitive to high-fat diet (HFD) effect on body weight. Especially, C57BL/6 mouse strain fed with HFD consistently produces severe obesity and hyperinsulinimia (Black et al., 1998). Severity of obesity is dependent of dietary fat contents. HFD consumption is believed to be the most common cause for obesity in humans, even more so than genetic predisposition (Hill and Peters, 1998). Therefore, this model can better mimic the pathological changes in obese humans.

CONCLUSION

All animal models utilized in the study of eating disorders are based on clinical symptoms. The difficulties of designing appropriate animal models in eating disorders are several. First, their definitions are overlapped under current diagnostic criterion. For example, BN and BED have very similar criteria and distinction is whether binge eating behavior is associated with inappropriate compensatory mechanism such as self-induced vomiting. Unfortunately, this is not a behavior that can be easily reproduced in animal models. More importantly, the etiology of eating disorders is not clearly defined. This is partially due to their complicated and multifactorial nature, which can be influ-

enced by social, personal, genetic, and environmental factors (Mathes et al., 2009; Oldershaw et al., 2011; Ploog and Pirke, 1987; Russell, 1979; van Hoeken et al., 2009; Wolfe et al., 2009). Current animal models obviously do not encompass all of these features, but they have contributed to the current understanding of eating disorders in different ways and to different degrees. Therefore, many variations of different animal models are introduced, and it is important to understand both the utility and the limitations of current models. Recent advances in biomedical sciences and the ability to use genetics as a tool for understanding diseases have helped scientists develop many genetic animal models that mimic human diseases. One example, the Cre/LoxP system, enables us to manipulate the gene expression in temporal and spatial manner. Moreover, gene–environmental interaction has been also emphasized in eating disorders. The recent discoveries and research in epigenetics have gained popularity among the scientific community. It would be a valuable tool in the characterization of eating disorders and treatments. Identification of epigenetic changes, which are often influenced by environmental changes, in the aforementioned animal models would be extremely useful in our understanding of disease progression and heritability. Advances in the etiology, onset, and progression of eating disorders are likely to be paramount in proper animal model development for the future.

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